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Case report

Reversible suicidal ideation after exposure to lacosamide

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1. Introduction

Patients with epilepsy have a threefold risk of completed suicide,[1] and a twofold risk of suicidal ideation[2] compared to normal controls. The causes are not well understood, although some risk factors such as pre-existing psychiatric disorders and epilepsy surgery have been identified.[3]

A metaanalysis conducted by the US Food and Drug Administration (FDA) based on 199 placebo-controlled antiepileptic drug (AED) trials with approximately 28,000 patients in the active arms, and approximately 16,000 patients in the placebo arms reported an increased risk for suicidality in the actively treated patients (odds ratio 1.8).[4] However, this meta-analysis did not distinguish between different substances or AED classes. In addition, a metaanlysis using studies with the same AED substances in patients with bipolar disorders could not find increased suicide risk in AED use compared with use of Lithium or non-AED substances.[5] All comparable analyses are hampered by a relatively low event rate resulting in wide confidence intervals. Thus, the contribution of individual AED substances to the risk of suicide or suicidal ideation remains unclear.

Lacosamide is a relatively new AED that is thought to exert its anticonvulsant effect by modulation of voltage-dependent sodium channels.[6] During the large mandatory placebo-controlled studies needed for licensation, depression or suicidal ideation was rare and no difference was found between the active arms and the placebo arms of the studies. In contrast to some other AED such as levetiracetam, phenobarbitone, topiramate or zonisamide where pre- and post-marketing data suggested increased risk of depression,[7,8] no such signal exists for lacosamide.

We report a patient with refractory partial epilepsy who experienced reversible phase of mood instability and suicidal ideation after exchanging levetiracetam by lacosamide.

2. Case report

We report the case of a 47-year-old man suffering from partial epilepsy since 31 years. His seizures start with visual sensations followed by loss of responsiveness and oro-alimentary automatisms and finally clonic movements of the left face and arm. His seizures had been refractory to phenytoin, valproate, lamotrigine, carbamazepine, levetiracetam, and oxacarbazepine. In October 2011, he underwent long-term video-EEG-monitoring. His typical seizures could be documented associated with right-hemispheric EEG seizure patterns, but additionally there were subclinical seizures arising from the left temporo-parietal region. Interictal EEG showed frequent intermittent slowing in the right temporal region, and spikes arising predominantly from the right anterior temporal region, more rarely from the left temporal region. MRI demonstrated bilateral nodular heterotopias bordering to both lateral ventricles. Therefore, he was not thought to be a candidate for epilepsy surgery. During the video-EEG monitoring, levetiracetam had been tapered off and oxcarbazepine was reduced to increase the chance of seizure occurrence. Immediately after finishing the video-EEG-monitoring, oxcarbazepine was increased to its old daily dose of 1500 mg, and levetiracetam was substituted by lacosamide. During the remaining few days of in-patient treatment, lacosamide was increased to its target dose of 400 mg per day (200 mg b.i.d.). During the rapid titration, the patient experienced mild tiredness that ceased after 2 days. He underwent neuropsychological testing that demonstrated decreased memory abilities for verbal material and deficits in verbal fluency, but average to high average abilities in most other categories. At that point, Beck's depression inventory (BDI) was performed and showed no evidence for depressive tendencies (7 points in BDI). He had never undergone psychotherapy, other psychiatric therapy, or counselling, in his life. He was discharged without complaints on October 18th. Two weeks after discharge, he presented in the epilepsy outpatient clinic and stated that he had not experienced any seizures nor any unwanted side effects of the medication. Serum levels of oxcarbazepine and lacosamide were 17.8 mg/l (10-OH-metabolite) and 5.6 mg/l, respectively. On

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December 13th, he was seen again in the outpatient clinic. He reported two seizures since the last visit, and complained of mild tiredness approximately 2 h after morning intake. His routine EEG showed no changes to the interictal EEG documented during presurgical video-EEG monitoring. He was told to split the morning dose of both lacosamide and oxcarbazepine and take one half in the morning, the other half at noon. At that visit, he seemed to be balanced and at ease with himself. No psychiatric symptoms were detected.

On December 31st, the patient presented at the emergency department of the hospital. He told that in the past week, he increasingly had experienced mood swings with predominantly depressive thoughts that he had never experienced before. In addition, he reported suicidal thoughts with death wishes that were completely new to him and frightened him because they seemed unnormal to him. During examination, his mood was depressed, he was tense and lacked his usual drive. He was admitted to the neurology ward because a drug side effect was assumed. Lacosamide was stopped, and levetiracetam was reinstituted at the formerly well-tolerated dose of 2000 mg/d (dose at admission to video-EEG monitoring in October 2011: 4000 mg/d). After 3 days, he had recovered completely. He did not show any mood abnormalities and stated that he felt like usual again. He declined any suicidal thoughts. After thorough psychiatric evaluation by an independent psychiatrist, he was discharged. During the following two weeks, levetiracetam was tapered and pregabalin was added, starting with 75 mg twice per day. Afterwards, he was seen every 6–8 weeks in the outpatient clinic. During the complete follow up until September 2012, i.e. 9 months after the incident, he did not show any sign of depression again. At each of his regular outpatient visits, he was asked about suicidal thoughts, and always declined them. His mood was stable and he seemed balanced in spite of his ongoing seizures that could not be controlled with his current combination therapy consisting of pregabalin (600 mg per day) and oxcarbazepine (1200 mg per day). Repeated routine EEG did not show any differences to the recordings before and during lacosamide intake.

3. Discussion

This patient experienced a sudden episode of depression and suicidal ideation that was clearly associated with the new onset therapy with lacosamide. Although no formal psychiatric evaluation had been performed before initiation of lacosamide, standardized testing (BDI) showed no evidence for a comorbid mood disorder, and there was no family history of suicidal ideation. In addition, none of the established risk factors for suicidality in patients with epilepsy such as newly diagnosed epilepsy or recent epilepsy surgery[3] was present. No mood-stabilizing agent had been tapered off, and no negative pharmacokinetic effect reducing the efficacy of a potential mood stabilizing AED could account for the symptoms. To the contrary, the drug preceding lacosamid was levetiracetam, a substance that is associated with an increased risk of depression.[8] The complete reversibility of the symptoms after cessation of lacosamide also speaks in favour of a causal relationship between the suicidality and the substance.

Lacosamide was titrated in a rapid fashion. This could have contributed to the occurrence of the symptoms. However, there was a time lag of more than 6 weeks between titration and symptom onset. Therefore, it seems unlikely that the speed of titration was a significant risk factor. Unfortunately, serum levels for lacosamide during the suicidal episode are not available. Therefore, accidental overdosing or decrease of clearance cannot be ruled out completely.

This is a single case report, thus one cannot draw conclusions as to a systematic effect of lacosamide on mood and depression. Since approval of the drug, there have been unpublished cases of depression and/or suicidal behaviour that have been included in the current physician's manual. In addition, behavioural problems have been seen in children treated with lacosamide.[9] However, systematic data are still missing for this (as well as other) substance(s). Standardized screening for suicidality should not only performed in the pivotal phase III studies, but should also be mandatory for post-marketing surveillance of anticonvulsants as well as for other substances acting in the central nervous system.

Conflicts of interest

Dr. Kellinghaus received honoraria and travel support from UCB, Eisai, Pfizer, Desitin, Novartis and Sanofi-Aventis. He has served on advisory boards for UCB and Eisai.

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